EPIDEMIOLOGY: ITS SCOPE AND LIMITATIONS FOR INDOOR AIR QUALITY

by KARL UBERLA

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Science is inherently controversial, particularly when it reaches its thresholds. Specifically, this is the case with low risk associations based on epidemiologic and toxicologic evidence. Examples of low risk associations in the control of indoor air quality are formaldehyde, asbestos, radon and "passive smoking". When SNOW in Great Britain analysed the association between cholera and water supply in the last century by epidemiologic methods, the relative risk was much larger. Today we are mainly concerned with low risk associations.

In my paper I will first address the scope of epidemiology and some of its basic limitations. In the second part I will deal with a case study of pas-

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sive smoking. Does passive smoking cause lung cancer? What is the contribution of epidemiology to this question? Such a case study provides a fair idea of the problems in low risk estimation by epidemiologic and toxicologic methods.

Toxicology and epidemiology are partners in the assessment of risks. Toxicology ascertains whether a risk in man can exist. Epidemiology ascertains whether there is a risk in man and what the size of the risk is. The relation between toxicologic methods and epidemiologic methods is important. On what line of thought should we rely? From a scientific point of view toxicologic data can only show whether there can be a risk in man. Epidemiologic methods alone can show whether there really is such a risk in man and what the magnitude of such a risk is. The latter cannot be inferred from toxicology data.

1. THE SCOPE OF EPIDEMIOLOGY

There are some twenty definitions of epidemiology, which vary to some extent. I use here the definition by MACMAHON (1970): Epidemiology is the study of the distribution and determinants of disease frequency in man. This definition -like others- contains, on the one hand, the distribution of diseases and health in populations, the descriptive part of epidemiology. On the other hand, it contains the search for the causes and determinants of diseases, implemented by analytic epidemiology. Epidemiology has a rich history. It uses nowadays complicated statistical models. Descriptive and analytic methods both contribute to the evidence.

Epidemiology starts from available data. Widely used data are vital records and death certificates, morbidity surveys, data from disease notification and registration and dedicated studies. Basic characteristics of persons are used in epidemiologic studies. Such characteristics are age, sex, race and nationality, marital status, occupation and socioeconomic status. There are a host of other variables to be considered, but experience has shown that these are important for most studies.

Epidemiology studies the variation in time. Variation in time can hint at the factors underlying diseases. There are point epidemics, which are limited to space and time. There are secular changes and cyclic fluctuations and there exist sometimes clusters in time. Variations in place are very im-

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portant to epidemiology. Differences in disease frequencies between countries can be partly attributed to socioeconomic and other differences between nations. International comparisons are therefore a useful instrument. Also the variation within a country can be an important source of our knowledge. The study of migrant populations -for instance the diseases of Japanese immigrants and their offsprings in the United States- offers an especially interesting source of epidemiologic evidence.

There are various study types in epidemiology. To make things simple I mention only two basic ones: cohort studies and case control studies. In cohort studies one starts in the present and observes into the future. In a defined group of people the exposure is assessed -for instance with environmental tobacco smoke (ETS)- and the lung cancer cases are observed in the following years. When performed properly such studies give good evidence. They need large numbers and are expensive. One can estimate incidences from such studies, one can estimate relative risks and one can also ascertain the attributable risk.

Case-control studies start with the cases and for every case one or several "controls" are selected. In both groups one tries to assess the exposure from history. This implies certain weaknesses. One can calculate a so-called odds ratio from such studies, which is an approximation of the relative risk in the case of low risk. One has to be careful in interpreting such studies for a variety of reasons. They are disturbed by bias, that is, systematic error. The memory is very susceptible to modifications of the reality. The controls might not be fair, confounders cannot be excluded and so on. However, case-control studies are not so expensive. One often has no other choice than to rely on the weaker evidence provided by such studies.

I want to mention three problems. Bias is a systematic error, which can occur in all epidemiologic studies. It is basically defined by the difference between the true value and its estimator. There are various sources and types of bias, for instance selection bias, interviewer bias and so on. Confounding means that the exposure-disease relationship is mixed up with the effects of extraneous variables. If such variables are observed, confounding can be controlled for, at least in principle. Misclassification means that a person is wrongly counted in a certain group, when he or she belongs to another group. A systematic trend in misclassification is called differential misclassification, which can give rise to wrong estimates of relative risk.

We use three different risk measures in epidemiology: incidence, rela-

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tive risk and attributable risk. The incidence is the ratio of those getting a disease or experiencing an event during a certain time span in relation to those at risk. The relative risk is the ratio of two incidences: the incidence in those with a defined risk and the incidence in those without the risk. The relative risk is independent of the size of the incidence. So it does miss an important part of the information on the risk. Another risk measure is the attributable risk. It is a difference of incidences: the incidence of those under risk minus the incidence of those without risk. Basically this is the number of additional deaths which are caused by the exposure in a defined population. The attributable risk can only be used when one knows that there is a causal relation between exposure and event. Otherwise the attributable risk is a speculation. One must stress that these three risk measures should not be used separately. They are connected by definition and they should be viewed together since each of them contains only part of the information on risk.

A statistical association does not imply a causal relation. One has to keep this in mind. A statistically significant association is from the very beginning fictitious. It has often nothing to do with causal connection. We had for instance in our country during a certain time a statistically significant association between the number of nests of storks and the number of babies born, which clearly is an artifact. Causal influence is approached by exclusion of other explanations. There are well-known criteria which must be fulfilled in their majority, if one wants to infer a causal connection between exposure and effect from epidemiologic data. These criteria for a causal inference from epidemiologic studies were proposed by Bradford-Hill and have been modified. They are criticized nowadays by some epidemiologists. Only a few causal connections remain acceptable when one sticks to these criteria. They are very basic and can be relied upon. They surely are acceptable to scientifically oriented persons. However, they should not be used like a simple checklist:

- There should be consistency of association in the available studies.
- The results should be similar in the same circumstances and should be replicable.
- The strength and the intensity of an association is an indicator for causality. A causal connection is less probable with a low relative risk of 2 than with a high relative risk of 5 or 10.

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- There should be specificity of association. Exposure, effect and way of action should be specific. This means that the exposure and the effect must be measured in a reliable and valid way.
- There should be a dose-response relationship. With higher doses there should be larger effects, at least in a certain dose range.
- The temporal relation between exposure and event should be such that the effect can be caused by the exposure. In cancer the latency period between exposure and event is 15 years and longer.
- Bias and confounding should be carefully excluded.
- There should be an impact of intervention. Removing the exposure should lead to a reduction of the risk, as was the case in the British doctors' study on the cessation of smoking and lung cancer.
- Finally, there should be biological plausibility.

Applying those criteria, one usually ends with limited or inadequate evidence. The International Agency of Research on Cancer (5) has used those criteria and proposed four levels of epidemiologic evidence in cancer research:

1. Sufficient evidence of carcinogenicity. There is a causal relationship between the exposure and human cancer.
2. Limited evidence of carcinogenicity. A causal interpretation is credible; however, alternative explanations (such as chance, bias and confounding) cannot be adequately excluded.
3. Inadequate evidence. There are few pertinent data or the available studies, while showing evidence of association, do not exclude chance, bias or confounding.
4. No evidence. Several adequate studies are available which do not show evidence of carcinogenicity.

Epidemiology as far as it is a science should adhere to stringent criteria. Otherwise it will become the playing ground for time-dependent opinions and prejudices. It is as honest to adhere to the null hypothesis as it is honest to accept the alternative hypothesis. In science the proof of the alternative hypothesis relies on those who propose it. In regulation one has to act before one knows exactly. This difference between knowledge and action is important. As scientists, we should not act before we know at least something.

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2. SOME BASIC LIMITATIONS IN EPIDEMIOLOGY.

In epidemiology we are concerned with complicated questions. As in other sciences, there are serious limitations.

A first limitation is that adequate studies are usually not available. In most cases one ends up with very limited data with respect to the hypothesis in question. Epidemiologic studies, if properly conducted, take a long time. So data are missing and adequate evidence is not available.

Often the validity of the exposure and of the endpoint measures is low. Proxy variables are used, which might not correlate well with what we intend to measure.

Adequate studies need huge numbers and consequently are very costly. There are many important questions and only a very small part of them can be investigated. Epidemiologic research has to be centered on a few questions. In our time, the important questions are questions of low risk associations. The high risks -smoking, infections and so on- have been studied and can be studied easily when new problems arise. When the effect is small in comparison to chance, bias and confounding, we are in trouble.

In addition, there are conflicting group interests in all societies. Consequently, studies can be financed or not, can be interpreted in different ways and can be brought to the attention of the public and the legislative bodies or not. Scientists in epidemiology must stay independent, for instance from industry and from public pressure groups, sometimes even from governmental agencies. As scientists we have to rely on clear facts and not on opinion.

As in other sciences there are thresholds for human perception and knowledge in epidemiology. There are mainly two reasons for such thresholds: in order to recognize a small risk, one needs huge numbers. Random noise creeps in. We simply cannot observe one million people over 20 years without dropouts, losses and missing data. So the results are not reproducible. On the other hand we have to live in case-control studies with bias and confounding. Therefore, relative risks smaller than 2 are generally difficult to reproduce. They are then beyond the threshold of human perception and knowledge. Incidences smaller than 10^{-5} to 10^{-6} can usually not be reproduced in cohort studies. They are then beyond the threshold of human perception and knowledge.

There are also thresholds for human perception in toxicology. Inferring from animal to man is such a threshold. In toxicology we have the paradigm

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of a missing threshold for carcinogenic substances. However, this paradigm is disputed more and more. A single molecule does not always meet its receptor and a single radiation quant does not always hit a target. So there must be cases in which there is an individual threshold. Furthermore there are repair mechanisms at nearly every level of carcinogenesis. For promotors the paradigm of a missing threshold has already been modified. In my opinion, the concept of a missing threshold for initiators will also disappear and will be replaced by more sophisticated models.

3. PASSIVE SMOKING AND LUNG CANCER: A SHORT CASE STUDY

There is no doubt that active smoking can cause lung cancer. Mainstream smoke contains a variety of carcinogens. A very high percentage, 90-95%, of lung cancer cases are smokers. A wealth of epidemiologic evidence shows a high risk increase with active smoking. There is hardly another single behavior which could be changed -like stopping smoking- which would have a comparable beneficial effect on the health and life expectancy of exposed populations. Stopping alcohol consumption could produce a beneficial effect of the same size order. Therefore, it is reasonable to try to reduce the exposure to carcinogens by active smoking, as it is reasonable to try to reduce the exposure to alcohol.

Lung cancer rates have been increasing in most countries since the beginning of the century when lung cancer was a very rare disease. The rates are much lower among women. During the last decades lung cancer has also increased among women. The most important risk factor for lung cancer is active smoking. Other risk factors are asbestos, radon, tuberculosis or genetic factors, but they are less important. DOLL and PETO estimate that about 90% of the lung cancer cases in men can be attributed to active smoking. Lung cancer leads to death in a very short time. One year after diagnosis only about 33 % still live, after five years only 10%. When lung cancer is diagnosed, the fatal destiny goes on.

There is very little known about the exposure of non-smokers to ETS. We looked at it in a representative sample in 1983 in Germany (7). Non-smoking men are exposed 1.20 hours a day in the working place, non-smoking women 0.40 hours. Considering only working non-smokers, men are

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exposed 2.00 hours a day, women 1 hour per day, that is 8.3 and 4.3 percent of the total time. One has to consider that only 42% of the population are never-smokers in our country and that the real values are lower due to the method of data collection.

The question is whether passive smoking causes lung cancer. There are other unhealthy effects of passive smoking, like cardiovascular effects, bronchopulmonary effects in children and effects on the unborn child during pregnancy. I restrict myself to the case of passive smoking and lung cancer. The National Research Council (9) and the Surgeon General of the United States (10) have stated that there is or there might be a causal relationship. Also, the German Research Foundation followed this path, which is mainly based on reasoning by analogy.

The best available study is the study of HIRAYAMA (2,3,4). I will try to show how weak the evidence from this study is. The original data are given in Table 1.

TABLE 1: SMOKING HABIT OF HUSBAND BY AGE OF WIFE. ORIGINAL DATA.

WIVES	HUSBAND'S SMOKING HABITS			
	NON	1 - 19	20 +	TOTAL
40-49	4 7918	21 17492	21 12615	46 38025
50-59	14 7635	46 15640	31 8814	91 32089
60-69	16 6172	31 10381	10 3793	57 20344
70 +	3 172	1 671	2 292	6 1082
TOTAL	37 21895	99 44184	64 25.461	200 91540

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Married non-smoking women aged 40 and above -91,540 from a cohort of 265,118 adults in Japan- were asked whether they were smokers, and their husbands were also asked about their smoking habits. The women were followed for 15 years and their death certificates were collected. 200 women died of lung cancer. The table shows the numbers in the age groups according to the smoking habits of the husband. There are only six lung cancer cases in the highest age group, in which the majority of lung cancer cases occur in the population. From these numbers relative risks were calculated. The point estimate of the risk ratio in the group of the women married to men smoking more than twenty cigarettes per day was 1.56 to 1.79, depending on the way of standardization. There was a dose-response relationship which was also significant.

Why is this particular study not conclusive?

The study was not designed to test this hypothesis, but to screen for a wide variety of possible risk factors. It therefore cannot prove the hypothesis. The cohort was not representative of the population. There was an age selection bias. The indicator by which the exposure was measured -being married to a man who smokes- was neither reliable nor valid, nor specific. Also the endpoint was not assessed with validity. We know from experience that lung cancer diagnosis on the death certificate might be erroneous. Confounding factors were not adequately considered, for instance working place, air pollution or medical care. Bias in registering the fact that a woman was a non-smoker was neither controlled nor excluded. Differential misclassification is likely, since in 1965 smoking women were very rare in Japan. Almost nothing is known on the 200 cases. Case reports are missing; autopsy and histology are available in only 11.5%.

Each of these arguments alone could invalidate the results. HIRAYAMA at a recent conference refused to give his material to other researchers for a re-analysis. The core of evidence in the HIRAYAMA study is that during 1965, 200 women in Japan told an interviewer on a single occasion that they were non-smokers, and their husbands said that they were smokers -which could have been different before and thereafter- and their death certificates subsequently contained the -perhaps erroneous- diagnosis of lung cancer. This information is not a convincing scientific data base. I published these and other arguments in 1987 (11).

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TABLE 2: DIFERENCES IN AGE DISTRIBUTION

AGE	PERCENT FEMALE POPULATION	PERCENT HIRAYAMA COHORT
40 - 49	42	42
50 - 59	32	35
60 - 69	20	22
70 +	6 *	1
	100	100

* In the female population 1965 in Japan over 40 there are 12 percent over 70 years old. We assumed here half ot them were still married with a living husband.

Recently we re-analysed the HIRAYAMA data (1) as far as they were published. Table 2 shows the differences in the age distribution between the female population in Japan in 1965 and the HIRAYAMA cohort. Only 1% in the cohort are older than 70 years in comparison to 12% in the population. We reduced this 12% to half -6%- assuming half the women were still married to a living man. It is obvious that there is a strong selection bias by age. When one removes this selection bias -I cannot go into details of calculation here- the relative risks become smaller and are no longer significant.

The first line of Table 3 shows the relative risk as calculated by HIRAYAMA, standardized by age of women only. In the 20+ group it is 1.56 and just significant at the one-tailed 5% level. Correcting for age selection bias the relative risks are much smaller and no longer significant. Considering subgroups -for instance women married to farmers and industry workers- only in the group of industry workers a high relative risk is present

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TABLE 3: RELATIVE RISK IN THE HIRAYAMA STUDY

	HUSBANDS SMOKING HABITS		
	NON	1-19	20 +
RR HIRAYAMA*	**1.00**	**1.37**	**1.56**
IL_{90}		1.00	1.11
RR CORRECTED**	**1.00**	**1.03**	**1.29**
IL_{90}		.77	.94

* Standardized by age of women only
** Age selection bias removed, standardized by age of women
The corrected relative risks are small and no longer significant

after removing the age selection bias. This can be explained by the fact that women married to industry workers might be exposed also to other risks. If one leaves the women married to industry workers out, the relative risk is no longer different from unity. It also decreases considerably by assuming moderate numbers being differentially misclassified. I think this shows that the relative risk of non-smoking women married to men who smoke is not significantly different from unity, provided one considers age selection bias and misclassification. We have published this (1), but other epidemiologists do not share our view.

Another large prospective study from GARFINKEL in the US could not show a risk increase. I carefully evaluated the available studies last year

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and published the evidence with a critical view (11). I cannot describe the 10 case-control studies here in detail. They all have much weaker evidence compared to the HIRAYAMA study.

Nowadays, so-called meta-analysis are used to summarize the evidence from various studies in a formal way. This is useful when studies are similar, especially with controlled clinical trials. However, false plus false does not equal right. Meta-analysis are only valid when the studies included have some minimal quality. The discussion on meta-analysis in this field was started by a paper by WALD et al. (12) two years ago, in which 12 studies are summarized to a significant relative risk of 1.35. The report of the National Research Council and of the Surgeon General in the US followed this publication, the authors being partly the same. Also, the German Research Foundation could not refrain from adding incomparable studies to a single point estimate of risk.

We did our own meta-analysis of the same studies (8). As you can see from Table 4 we grouped the studies according to quality - whether histology was present, whether the exposure measure was somehow critically judged - and we gave a grade from 2 - 6 for overall methodological quality to every study. The study of TRICHOPOULOS got a grade 6 -the worst rating-, the study of GARFINKEL a 2 -our best rating. In the last column we decided for case control studies, whether a single study was of quality+ or of quality- according to these criteria.

In table 5 you see some of our results. The HIRAYAMA study was included with the relative risk corrected for age selection bias. We included women only, since men inflate only the denominator. We also left out the previous smokers in the studies of TRICHOPOULOS and KOO. All resulting relative risks are not different from unity, with the exception when one considers only the 4 case control studies of lower quality. Considering all 12 studies, the relative risk is 1.12. Leaving TRICHOPOULOS out gives 1.08. This study is a textbook example of how a case-control study should not be conducted and analysed. Introducing some cautious assumptions on misclassification, the numbers are still smaller. Also LEE (6) has remarked in his papers that at least part of the evidence can easily be explained by differential misclassification. One can look at the possible meta-analysis in a different way. With 10 case-control studies there are 1023 possible combinations

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TABLE 4: QUALITY RATING OF STUDIES SELECTED FOR META-ANALYSIS

Author	Histology	Exposure	Quality Rating*	Resulting Group
HIRAYAMA	–	–	3	Cohort
GARFINKEL	–	–	2	Cohort
CHAN et al.	+	+	4	CC Quality +
CORREA et al.	–	–	5	CC Quality –
TRICHOPOULOS et al.	–	–	6	CC Quality –
BUFFLER et al.	+	–	4	CC Quality +
KABAT et al.	+	+	4	CC Quality +
GARFINKEL et al.	+	+	4	CC Quality +
AKIBA et al.	–	–	5	CC Quality –
LEE et al.	–	+	5	CC Quality –
KOO et al.	+	+	4	CC Quality +
PERSHAGEN et al.	+	+	4	CC Quality +

* 2 = acceptable, 3 = possibly flawed, 4 = bias and confounding suspected, 5 = major bias and confounding suspected, 6 = unacceptable.

The included studies are the same as in the paper by WALD et al. (1986) and by LETZEL and UBERLA (1988). We included women only.

for meta-analysis. Only 24 of them -2.3%- are technically significant. They are dominated by three studies of low quality, mainly by the TRICHOPOULOS study. All this shows that meta-analysis are very sensitive to the included data, that such sensitivity analysis give some insight into the combination of studies and that they presently do not contribute to our overall evidence regarding passive smoking and lung cancer.

Whether passive smoking causes lung cancer is an open question today. It is therefore not scientifically sound to calculate the attributable risk, i.e. the possible number of deaths attributed to passive smoking per year. All serious scientists refrain from such calculations. Of course, it cannot be ex-

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TABLE 5: SUMMARY OF META - ANALYSIS

HIRAYAMA STUDY CORRECTED FOR AGE SELECTION BIAS CAUTIOUS ASSUMPTIONS FOR MISCLASSIFICATION		
	ORIGINAL DATA	MISCLASSIFICATION ASSUMPTIONS
	RR	RR
ALL 12 STUDIES	1.12	1.04
11 STUDIES (WITHOUT TRICHOPOULOS)	1.08	.99
2 COHORT STUDIES AND 6 CASE CONTROL STUDIES QUALITY +	1.04	.97
6 CASE CONTROL STUDIES QUALITY +	1.07	.90
4 CASE CONTROL STUDIES QUALITY	1.67	1.43

All relative risks are not significant with the exception of meta-analysis for 4 case control studies of quality –

cluded that there is a causal relationship. If there is an effect, it is likely to be very small compared to other risks.

The majority of criteria for a causal connection are not fullfilled. There is no consistency, there is a weak association, there is no specificity, the dose-effect relation can be viewed controversially, bias and confounding are not

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adequately excluded, there is no intervention study, significance is only present under special conditions and the biologic plausibility can be judged controversially.

There is room for honest differences in opinion. The jury is still out. All epidemiologic evidence can be explained by bias, confounding, misclassification and chance, nearly in the same way as by accepting the alternative hypothesis. Overall, according to the levels of the IARC, there is only inadequate evidence.

Whether passive smoking causes lung cancer is a serious hypothesis. The majority of publications in the field is a little in favor of this hypothesis. However, as I have said, I personally prefer to stay with the null hypothesis for the time being, following my careful analysis of the available evidence.

What can we learn from such a case study in low risk association? Toxicological studies alone cannot provide evidence on the size of a risk to man from indoor air pollution. There is not a single animal study with ETS which succeeded in producing lung cancer. Epidemiologic studies are the way to ascertain whether there is a risk in man, and what the size of the risk is. There are thresholds for human perception and knowledge in epidemiology: relative risks smaller than 2 and incidences smaller than 10^{-5} to 10^{-6} are such thresholds. The concept of a missing threshold for carcinogens should be replaced by more sophisticated models, when one tries to assess the cancer risk of indoor air quality.

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